Persistent Fetal Sinus Bradycardia Associated with Maternal Anti-SSA/Ro and Anti-SSB/La Antibodies

PRIYA CHOCKALINGAM, EDGAR T. JAEGGI, LUKAS A. RAMMELOO, MONIQUE C. HAAK, PHEBE N. ADAMA van SCHELTEMA, JOHANNES M.P.J. BREUR, MARGOT M. BARTELINGS, SALLY-ANN B. CLUR, and NICO A. BLOM

ABSTRACT. ***Objective.*** To study the clinical course and outcome of fetal sinus bradycardia (SB) due to maternal antibody-induced sinus node dysfunction.

Methods. We reviewed the maternal, prenatal, and postnatal findings of fetuses with SB associated with elevated maternal anti-SSA/Ro and anti-SSB/La antibodies.

Results. Of the 6 cases diagnosed prenatally, 3 had isolated SB persisting after birth and had a good prognosis. Three fetuses with SB and severe myocardial involvement (congenital complete heart block and/or endocardial fibroelastosis) succumbed *in utero* in spite of treatment. Postmortem histopathology in 1 fetus showed inflammatory destruction of the sinus and atrioventricular nodes. SB was detected incidentally in a 7-year-old girl. She had intermittent heart block with progressive sinus arrest requiring permanent pacemaker.

Conclusion. Fetal SB associated with maternal autoantibodies may persist in childhood, with a good prognosis in the absence of widespread cardiac involvement. (J Rheumatol First Release Nov 15 2011; doi:10.3899/jrheum.110720)

Key Indexing Terms:
AUTOANTIBODIES FETUS SINUS BRADYCARDIA
HEART BLOCK PROGNOSIS

Maternal antibody-mediated fetal heart disorder, initially identified as congenital complete atrioventricular block (CCAVB), now encompasses a wider spectrum of manifestations including second-degree and transient fetal first-degree heart block, prolongation of corrected QT (QTc) interval, sinus bradycardia (SB), late-onset cardiomyopathy, and endocardial fibroelastosis (EFE)[1,2]. Maternal autoantibodies to SSA/Ro and/or SSB/La ribonucleoproteins are presumed to cross the placenta and cause cardiac injury in a previously normal fetus, independent of whether the mother has systemic lupus erythematosus or Sjögren's syndrome or is totally asymptomatic. Fetal bradycardia due to maternal antibody-mediated CCAVB has been extensively investigated. In contrast, the clinical course and outcome of fetal SB due to maternal antibody-induced sinus node dysfunction with or without atrioventricular conduction abnormalities is relatively unknown.

From the Departments of Pediatric Cardiology at Academic Medical Centre, Amsterdam; VU University Medical Centre, Amsterdam; Leiden University Medical Centre, Leiden; and University Medical Centre, Utrecht; Departments of Obstetrics and Gynecology, VU University Medical Centre, Amsterdam; Leiden University Medical Centre, Leiden; and Department of Anatomy and Embryology, Leiden University Medical Centre, Leiden, The Netherlands; and Fetal Cardiac Program, The Hospital for Sick Children, Toronto, Ontario, Canada.

P. Chockalingam, MBBS; S-A.B. Clur, PhD, Pediatric Cardiology, Academic Medical Centre, Amsterdam; E. Jaeggi, MD, Fetal Cardiac Program, The Hospital for Sick Children; L.A. Rammeloo, MD, Pediatric Cardiology, VU University Medical Centre; M.C. Haak, PhD, Obstetrics and Gynecology, Leiden and VU University Medical Centres; P.N. Adama van Scheltema, MD, Obstetrics and Gynecology, Leiden University Medical Centre; J.M.P.J. Breur, PhD, Pediatric Cardiology, University Medical Centre Utrecht; M.M. Bartelings, PhD, Anatomy and Embryology, Leiden University Medical Centre; N.A. Blom, MD, PhD, Professor, Pediatric Cardiology, Academic Medical Centre, Amsterdam, and Leiden University Medical Centre.

Address correspondence to Dr. N.A. Blom, Department of Pediatric Cardiology, Academic Medical Centre, Meibergdreef 9, 1100 DD Amsterdam, The Netherlands. E-mail: N.A.Blom@amc.uva.nl

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MATERIALS AND METHODS

Between 2000 and 2010, 98 fetuses with maternal antibody-associated cardiac conduction disease were followed in the 5 participating centers. We reviewed the maternal, prenatal, and postnatal findings of fetuses with SB associated with raised maternal anti-SSA/Ro and anti-SSB/La antibodies. A postnatally diagnosed case of SB is also reported here.

RESULTS

Isolated SB was diagnosed in 3 fetuses (Cases 1–3, Table 1). Mild right ventricular dilatation and dysfunction were observed in Case 1. During followup with serial fetal echocardiography, SB with normal atrioventricular conduction persisted. All 3 fetuses exhibited normal intrauterine growth and development, resulting in term deliveries. Postnatal cardiac evaluation with electrocardiogram (ECG), echocardiogram, and 24-hour ambulatory ECG (Holter) confirmed the fetal findings. The right ventricular dilatation and dysfunction seen in Case 1 resolved after birth. The mean 24-hour heart rate was 100, 84, and 81 bpm in the 3 cases at ages 3 months, 1 day, and 4 days of life, respectively, with Case 2 exhibiting atrial and junctional escape rhythm. This patient developed symptoms of reduced exer-

Table 1. Clinical characteristics of cases with maternal autoantibody-associated sinus bradycardia.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7*
Maternal age, yrs, history	31, G1P0	40, G4P0A3	35, G2P1	30, G1P0	34, G3P2	28, G1P0	NA
Anti-SSA/Ro	+	+	+	+	+	+	NA
Anti-SSB/La	+	+	+	+	–	+	+ (mother's serology)
GA at diagnosis, wks	21	25	25	19	20	18	7 yrs, female
Atrial rate	80–85	70–90	75–95	60–70	81	85	65
Ventricular rate, bpm	80–85	70–90	75–95	53	52	85	65
AV condition	Normal	Normal	Normal	CCAVB	CCAVB	Normal	1°AVB
Other findings	RV dysfunction	None	None	Hydrops	Hydrops, EFE, ventricular dysfunction	Hydrops, EFE, ventricular dysfunction	None
Treatment	None	None	None	Maternal steroid, ß-mimetic	Maternal steroid, ß-mimetic, IVIG	None	None
GA at birth, wks, mode of delivery	39, CS	37, VD	39, VD	30, IUD	25, IUD	18, IUD	NA
Clinical findings	SB	SB, junctional escape rhythm	SB	NA	NA	NA	SB and progressive sinus arrest by age 9 yrs
Age and heart rate (bpm) at last followup	15 mo, 81**	5 yrs, 50	2 mo, 80	NA	NA	NA	10 yrs, 57 (pacemaker)

G: gravida indicates the number of pregnancies including the current pregnancy; P: para indicates the number of viable births; A: abortus indicates the number of abortions. * Postnatal diagnosis. ** Normal resting heart rate for age is 90-110 bpm. AV: atrioventricular; AVB: atrioventricular block; bpm: beats per minute; CCAVB: congenital complete atrioventricular block; CS: cesarean section; EFE: endocardial fibroelastosis; GA: gestational age; IUD: intrauterine death; IVIG: intravenous immunoglobulin; NA: not applicable; RV: right ventricle; SB: sinus bradycardia; VD: vaginal delivery.

cise tolerance at the age of 5 years when his ECG showed a low heart rate of 50 bpm with mainly junctional escape rhythm (Figure 1A). There was no evidence of hepatic or hematologic involvement in any of the patients. However, cutaneous lesions of neonatal lupus were observed in Case 1 during infancy.

SB with severe myocardial involvement in the form of CCAVB and/or EFE with ventricular dysfunction was present in 3 fetuses (Cases 4–6, Table 1). Cases 4 and 5 succumbed *in utero* at 30 and 25 weeks of gestation, respectively, not responding to maternal treatment. Fetal demise of Case 6 occurred within 3 days of referral to the fetal cardiologist. Postmortem examination revealed a structurally normal heart with hypertrabecularization of the ventricular walls in Case 4, and the histopathology showed extensive fibrosis and calcification of the sinus and atrioventricular nodes with involvement of the entire conduction system (Figure 2).

A 7-year-old girl (Case 7, Table 1) was referred with irregular heartbeat detected during routine school examination. The ECG showed SB with a rate of 65 bpm, first-degree heart block (PR interval 382 ms), QRS duration

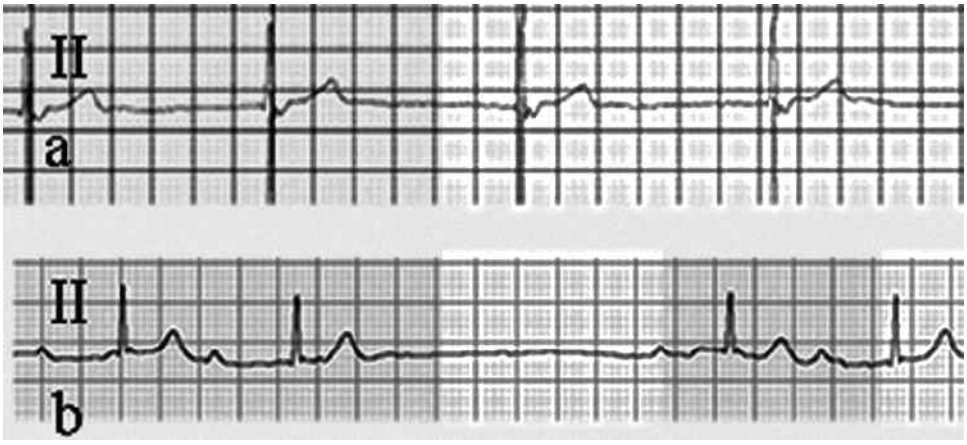

Figure 1. A. Case 2 at age 5 years. Lead II of 12-lead ECG (standard calibration) showing low heart rate of 50 bpm with mainly junctional escape rhythm in a child with persistent sinus bradycardia. B. Case 7 at age 9 yrs. Lead II of 12-lead ECG (half-standard calibration) showing first-degree heart block and sinus arrest.

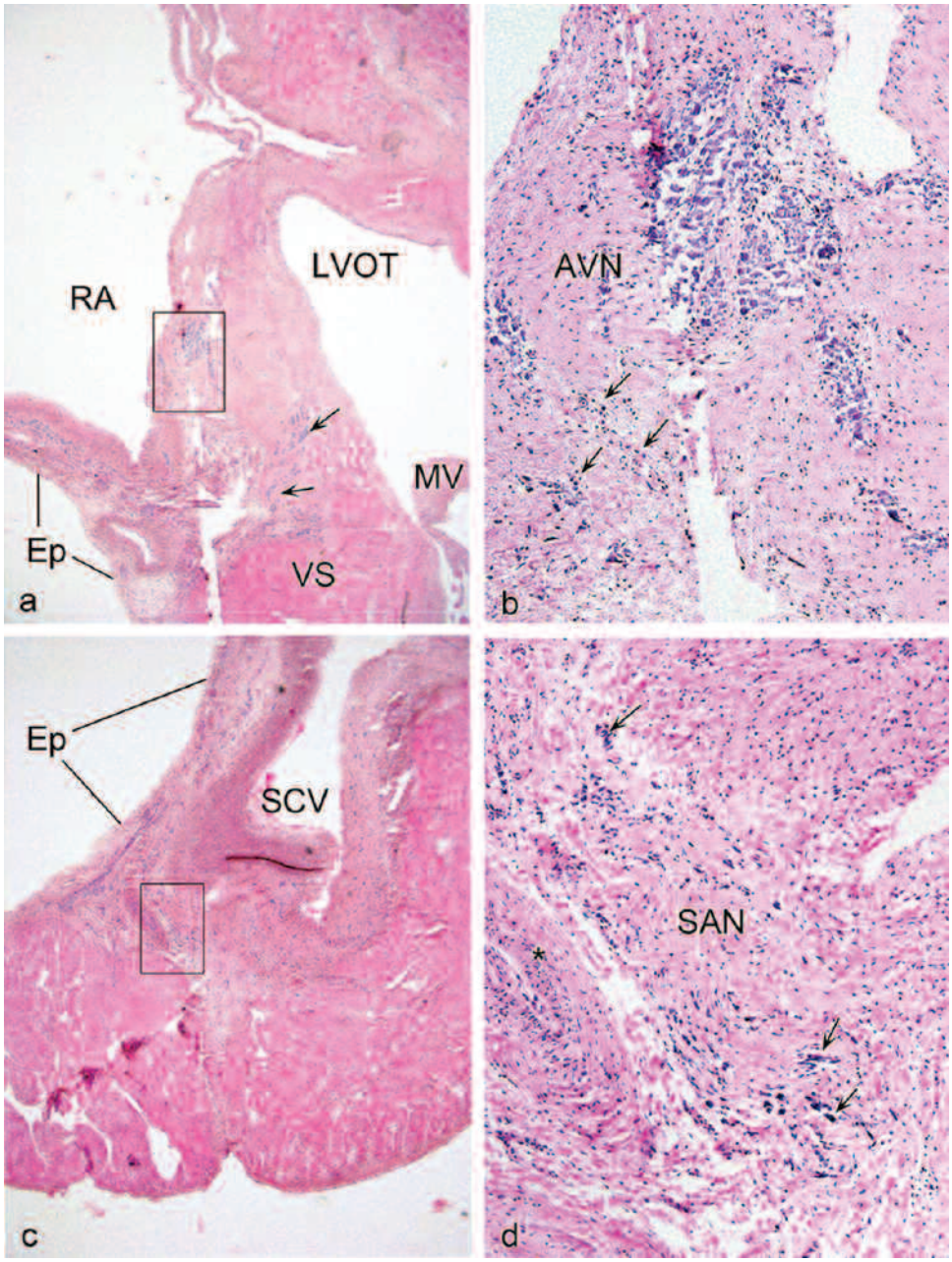

Figure 2. Case 4 at 30 weeks' gestation. Postmortem histopathologic examination of the fetal heart showing the area of atrioventricular node (AVN) in overview (A) and in enlargement (B) and the sinoatrial node (SAN) in overview (C) and in enlargement (D). Arrows indicate inflammatory cells. Dense blue area in B shows calcification due to the severe inflammatory process. RA: right atrium; Ep: epicardial surface; VS: ventricular septum; MV: mitral valve; LVOT: left ventricular outflow tract; SCV: superior caval vein. *Wall of the SAN artery.

94 ms, and QTc 380 ms. Holter ECG revealed an irregular sinus rhythm with first-degree and intermittent second-degree heart block (Mobitz type 1). During followup, progressive sinus arrest and atrial and junctional escape rhythm developed by the age of 9 years (Figure 1B). A permanent pacemaker was implanted at age 10 years for progressive sinus node dysfunction.

DISCUSSION

Immune-mediated destruction of the fetal cardiac conduction system by maternal autoantibodies is well recognized. However, our study showed that SB is a definite and persistent manifestation of the disease, and may either be isolated or part of a more widespread conduction abnormality. A functional basis for SB associated with CCAVB in mater-

nal antibody-induced fetal conduction defects was provided by Hu, *et al*[3]. An ionic mechanism of the negative chronotropic action of maternal autoantibodies was proposed by demonstration of a reduction in L-type and T-type Ca2+ currents in sinus nodal cells. Further biochemical and functional evidence for the autoimmune-associated SB was shown in humans by way of the "calcium channel hypothesis," where the neuroendocrine α1D Ca channel, which is a component of the L-type Ca2+ channel, is also inhibited by positive IgG[4]. Histopathological findings in our study are consistent with reports on involvement of the sinus node in the inflammatory response[5,6]. Beaufort-Krol, *et al* specifically studied the sinus node function in children with CCAVB and found it to be normal[7]. Menon, *et al* studied the chronotropic competence of the sinus node in cases of CCAVB and reported it was incompetent in 11% of the cases[8].

Maternal autoantibody-associated fetal cardiac disease is a spectrum of manifestations including SB[9,10,11]. In our centers, 98 fetuses with antibody-associated atrioventricular conduction abnormality were followed between 2000 and 2010. Isolated SB persisting after birth was present in 3% of cases and they all had a good prognosis. Regular fetal ECG monitoring would largely suffice in cases with isolated SB. The presence of CCAVB and/or EFE changes the management strategy and carries a relatively poor prognosis. Transient SB in the newborn has been reported[12,13]. However, the 3 cases we describe had SB persisting at the ages of 15 months, 5 years, and 2 months, respectively. Postnatal progression of the disease is possible and hence close monitoring is warranted to detect clinical and ECG signs of worsening conduction defects. SB can also present in a previously healthy child, as reported here. This child's mother was asymptomatic and had elevated anti-SSA/Ro and anti-SSB/La antibodies at the time of diagnosis. There is evidence supporting this persistence of antibody positivity in mothers well after initial detection during pregnancy[14]. The late presentation in the child may be explained by subclinical disease in prenatal and neonatal periods, with progression later.

The differential diagnoses of persistent SB in the fetus include congenital cardiac anomalies and congenital long QT syndrome. Thus evaluation should include fetal echocardiography and ECG. An ECG at birth should be a mandatory part of evaluation of neonates exposed to maternal anti-SSA/Ro and anti-SSB/La antibodies. As normal fetal echocardiography in fetuses exposed to maternal autoantibodies and normal ECG (and echocardiography) at birth has never been followed by a cardiac abnormality, parents could be reassured based on these findings. Qualitative antibody assays showed significantly elevated anti-SSA/Ro antibody levels in all our cases, consistent with previous findings[15].

Fetal sinus bradycardia associated with maternal autoantibodies may be permanent, but carries a good prognosis in the absence of widespread cardiac involvement.

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